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Inventor: Babish et al. Filing Date: Herewith Attorney Client-Matter No.: 68911-074 Tel: 858-535-9001

Induction of Cox-2 gene depends upon cell type. **Arachidonic Acid** Cyclooxygenase-1 MSAND COX-2 mRNA Gyclooxygenase-2 PĞG₂ Mitogens •Growth factors Cytokines •Bacterial lipopolysaccharide PGH₂ Reactive oxygen intermediates $\mathsf{PGF}_{\mathbf{2}\alpha}$ PGD₂ PGI₂

Array of eicosanoids produced depends upon cell type. Cellular response is a function of intracellular and extracellular receptors.

Inventor: Babish et al. Filing Date: Herewith Attorney Client-Matter No.: 68911-074 Tel: 858-535-9001

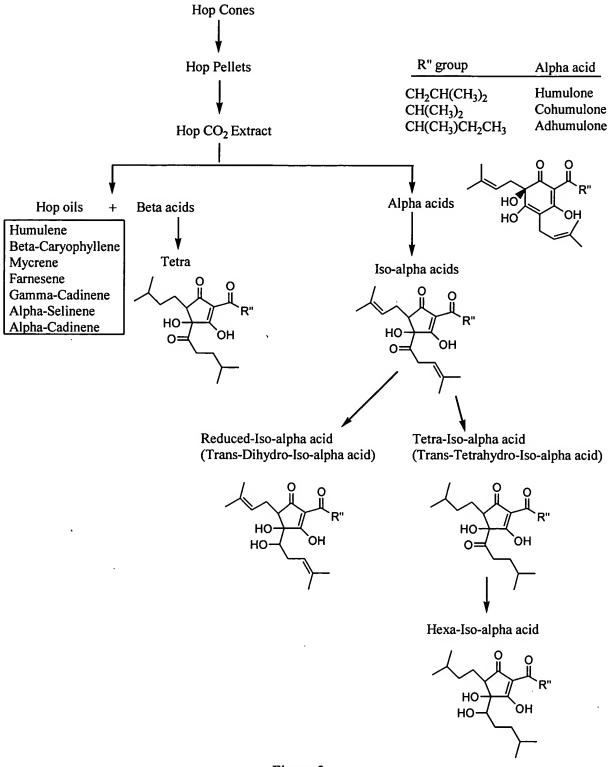


Figure 2

Title: SYNERGISTIC ANTI-INFLAMMATORY PHARMACEUTICAL COMPOSITIONS AND RELATED...
Inventor: Babish et al.
Filing Date: Herewith
Attorney Client-Matter No.: 68911-074
. Tel: 858-535-9001

$$[A] \begin{array}{c} H_3C \\ H_3C \\ H \end{array}$$

$$[B] \qquad \qquad \underset{\mathsf{H}_3\mathsf{C}}{\overset{\mathsf{H}_2\mathsf{H}}{\mathsf{OH}}} \overset{\mathsf{OH}}{\overset{\mathsf{O}}{\mathsf{O}}} \overset{\mathsf{O}}{\overset{\mathsf{O}}{\mathsf{H}}}$$

$$[C] \xrightarrow{H_3C} \xrightarrow{H_2} \xrightarrow{H_2} \xrightarrow{H} \xrightarrow{OH} \xrightarrow{O$$

$$[\mathbf{D}] \xrightarrow{\mathsf{H}_3\mathsf{C}} \overset{\mathsf{H}_2}{\mathsf{H}} \overset{\mathsf{H}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}}{\overset{\mathsf{OH}}}}{\overset{\mathsf{OH}}}}}{\overset{\mathsf{OH}}}{\overset{\mathsf{OH}}}}{\overset{\mathsf{OH}}}}}}}}}}}}}}}}}}}}}}$$

$$[E] \begin{array}{c} H_3C \\ H_3C$$

Figure 3

Title: SYNERGISTIC ANTI-INFLAMMATORY PHARMACEUTICAL COMPOSITIONS AND RELATED...
Inventor: Babish et al.
Filing Date: Herewith
Attorney Client-Matter No.: 68911-074
Tel: 858-535-9001

Figures 4 A-C

Title: SYNERGISTIC ANTI-INFLAMMATORY PHARMACEUTICAL COMPOSITIONS AND RELATED... Inventor: Babish et al.

Inventor: Babish et al. Filing Date: Herewith Attorney Client-Matter No.: 68911-074 Tel: 858-535-9001

Figures 4 D-F

Title: SYNERGISTIC ANTI-INFLAMMATORY PHARMACEUTICAL COMPOSITIONS AND RELATED...
Inventor: Babish et al.
Filing Date: Herewith
Attorney Client-Matter No.: 68911-074
Tel: 858-535-9001

A

B

$$H_3C$$
 CH_3
 CH_3

Figures 5 A-D

Title: SYNERGISTIC ANTI-INFLAMMATORY PHARMACEUTICAL COMPOSITIONS AND RELATED... Inventor: Babish et al.

Filing Date: Herewith
Attorney Client-Matter No.: 68911-074
Tel: 858-535-9001

$$\begin{array}{c} H \\ G \\ H_3C \\ \hline \\ N \\ \hline \\ CH_2-CH_2-CH_3 \\ \hline \\ CH_2-CH_3-CH_2 \\ \hline \\ CH_2-CH_3-CH_2 \\ \hline \\ \end{array}$$

Figures 5 E-H

Title: SYNERGISTIC ANTI-INFLAMMATORY PHARMACEUTICAL COMPOSITIONS AND RELATED... Inventor: Babish et al.

Inventor: Babish et al.
Filing Date: Herewith
Attorney Client-Matter No.: 68911-074
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Figures 5I-N

ĊH₃

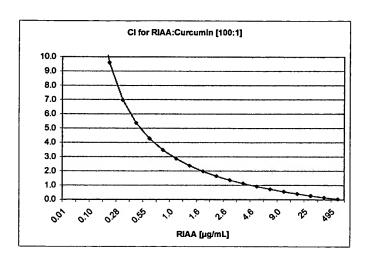
ĊH₃

 $\label{thm:compositions} \textbf{Title: SYNERGISTIC ANTI-INFLAMMATORY PHARMACEUTICAL COMPOSITIONS AND RELATED...} \\ \textbf{Inventor: Babish et al.}$

Filing Date: Herewith Attorney Client-Matter No.: 68911-074

Tel: 858-535-9001

_		RIAA	Curcumin
Fa	CI	[µg/mL]	[µg/mL]
0.02	68,336	0.01	0.000
0.05	28.842	0.04	0.000
0.10	14.609	0.10	0.001
0.15	9.589	0.18	0.002
0.20	6.984	0.28	0.003
0.25	5.376	0.40	0.004
0.30	4.277	0.55	0.006
0.35	3.475	0.73	0.007
0.40	2.862	1.0	0.010
0.45	2.375	1.2	0.012
0.50	1.979	1.6	0.016
0.55	1.649	2.0	0.020
0.60	1.369	2.6	0.026
0.65	1.127	3.4	0.034
0,70	0.916	4.6	0.046
0.75	0.729	6.3	0.063
0.80	0.562	9.0	0.090
0.85	0.409	14	0.139
0.90	0.269	25	0.247
0.95	0.137	63	0.629
4 00	0.004	400	4 0 00



Shaded area represents region of synergy

1.00

Figure 6A

RIAA:Curcu	min [10:1]		
		RIAA	Curcumin
Fa	CI	[µg/mL]	(µg/mL)
0.02	33.103	0.006	0.001
0.05	18.074	0.025	0.002
0.10	11.23	0.08	0.008
0.15	8.371	0.15	0.015
0.20	6.713	0.26	0.026
0.25	5.596	0.40	0.040
0.30	4.774	0.59	0.059
0.35	4.134	0.8	0.084
0.40	3.614	1.2	0.116
0.45	3.177	1.6	0.158
0.50	2.801	2.1	0.214
. 0.55	2.471	2.9	0.290
0.60	2.174	4.0	0.395
0.65	1.902	5.5	0.546
0.70	1.650	7.7	0.772
0.75	1.412	11	1,100
0.80	1.182	17	1.700
0.85	0.954	°30	3.000
0.90	0.718	60	6.000
0.95	0,457	188	18,600
1.00	0.172	2266	228.600

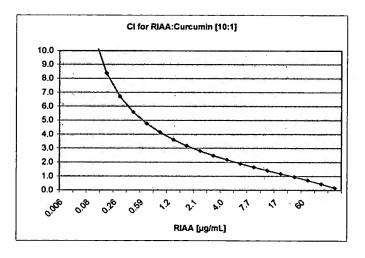
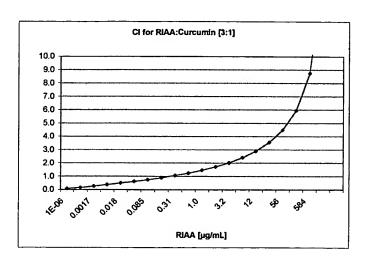


Figure 6B

Inventor: Babish et al. Filing Date: Herewith Attorney Client-Matter No.: 68911-074 Tel: 858-535-9001

RIAA:Curcumin [3:1]

		RIAA	4708
Fa	CI	[µg/mL]	[µg/mL]
0.02	0.073	0.000001	0.000
0.05	0.150	0.00020	0.000
0.10	0.268	0.0017	0.000
0.15	0.380	0.0070	0.002
0.20	0.497	0.018	0.004
0.25	0.622	0.041	0.010
0.30	0.756	0.085	0.021
0.35	0.904	0.17	0.041
0.40	1.069	0.31	0.077
0.45	1.256	0.56	0.14
0.50	1.472	1.0	0.25
0.55	1.726	1.8	0.45
0.60	2.031	3.2	0.81
0.65	2.410	6.0	1.5
0.70	2.894	12	2.9
0.75	3.546	24	6.0
0.80	4.479	56	14
0.85	5.957	153	38
0.90	8.732	584	146
0.95	16	5095	1274
1.00			



Shaded area represents region of synergy

Figure 6C

RIAA:Curcumin [3:2]

				RIAA	Curcumin
	Fa		Ci	[µg/mL]	[µg/mL]
	0.02		0.025	0.000004	
	0.05	3/4	0.062	0.00008	0.000
	0.10	: \$	~ 0.129	© 0.0008 🎄	0.000
š	0.15	~4	0.202	0.0032	0.001
	0.20	,	0.285	0.0093	0.004
	0.25		* 0.378 *	0.022	· 0.009
,	0.30		0.486	a 0.049 ·	0.020
	0.35		0.610	0.10	0.039
	0.40	.4	0.756	0.19	0.076
,	0.45	4	0.929	₹0.36	0.143
	0.50		1.138	0.7	0.266
	0.55		1.395	1.2	0.494
	0.60		1.719	2.3	0.928
	0.65		2.140	4.5	1.792
	0.70		2.707	9.1	3.624
	0.75		3.511	20	7.840
	0.80		4.739	48	19.200
	0.85		6.83	140	56.000
	0.90		11	582	232.800
	0.95		25	5830	2332.000
	1.00		156		0.000

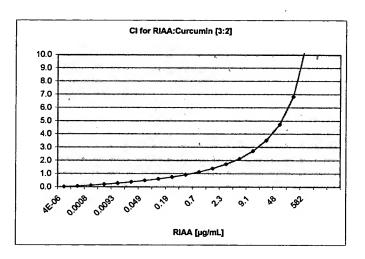
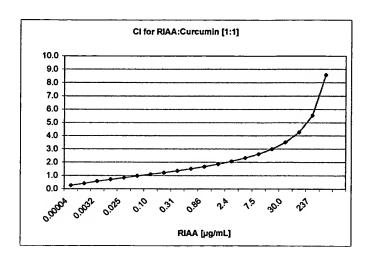


Figure 6D

Inventor: Babish et al. Filing Date: Herewith
Attorney Client-Matter No.: 68911-074

Tel: 858-535-9001

RIAA:Curcu	min [1:1]		
		RIAA	Curcumin
Fa	CI	[µg/mL]	[µg/mL]
0.02	0.267	0.00004	0.00004
0.05	0.408	0.00047	0.00047
0.10	0.575	0.0032	0.0032
0.15	0.715	0.010	0.010
0.20	0.844	0.025	0.025
0.25	0.971	0.052	0.052
0.30	1,098	0.10	0.10
0.35	1.230	0.18	0.177
0.40	1.369	0.31	0.307
0.45	1.518	0.52	0.517
0.50	1.683	0.86	0.864
0.55	1.868	1.4	1.440
0.60	2.077	2.4	2.435
0.65	2.324	4.2	4.200
0.70	2.625	7.5	7.530
0.75	3.006	14.0	14.000
0.80	3.518	30.0	30.000
0.85	4.268	73	73.000
0.90	5.546	237	237.000
0.95	8.569	1600	1600.000
4.00			



Shaded area represents region of synergy

Figure 6E

RIAA:Curcumin	[2:3]	
		۰

1.00

		RIAA	Curcumin
Fa	CI	[µg/mL]	[µg/mL]
0.02	0.181	0.000026	0.00004
0.05	0.377	0.00040	0.00067
0.10	0.682	0.0034	0.0056
* 0.15	0.991	** 10.013*	0.021 *
0.20	1.317	0.034	0.057
0.25	1.669	0.079	0.13
0.30	2.056	0.16	0.27
0.35	2.489	0.31	0.52
0.40	2.979	0.57	0.95
0.45	3.544	1.0	1.7
0.50	4.206	1.8	3.0
0.55	4.998	3.2	5.4
0.60	5.965	5.8	9.7
0.65	7.183	11	18
0.70	8.773	21	35
0.75	19.951	43	72
0.80			
0.85			
0.90			
0.95			
1.00			

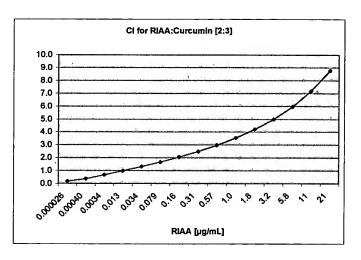


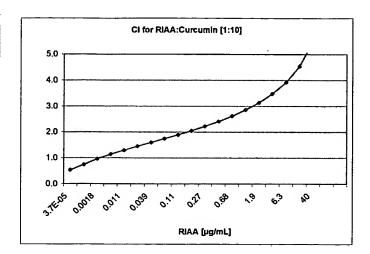
Figure 6F

Inventor: Babish et al. Filing Date: Herewith Attorney Client-Matter No.: 68911-074

Tel: 858-535-9001

RIAA:Curcumin [1:10] RIAA Curcumin

	Fa	CI	(µg/mL)	(µg/mL)
	0.02	0.539	0.000037	0.00037
	0.05	0.739	0.00032	0.0032
_	0.10	0.962	0.0018	0.018
	0.15	1.140	0.0051	0.051
	0.20	1.298	0.011	0.11
	0.25	1.449	0.022	0.22
	0.30	1.596	0.039	0.39
	0.35	1.744	0.07	0.65
	0.40	1.896	0.11	1.1
	0.45	2.056	0.17	1.7
	0.50	2.227	0.27	2.7
	0.55	2.414	0.42	4.2
	0.60	2.622	0.68	6.8
	0.65	2.860	1.1	11
	0.70	3.140	1.9	19
	0.75	3.482	3.3	33
	0.80	3.923	6.3	63
	0.85	4.538	14	140
	0.90	5.514	40	400
	0.95			
	1.00			



Shaded area represents region of synergy

Figure 6G

RIAA:Curcumin [1:100]

			RIAA	Curcumin
_	Fa	CI	[µg/mL]	(µg/mL)
1	0.02 & «	0.773	0.0000082	0.00082
à.	0.05	0.894	0.000055	0.0055
	0.10	1.006	0.00025	0.025
	0.15	1.083	0.00062	0.062
	0.20	1.145	0.0012	0.12
	0.25	1.200	0.0022	0.22
	0.30	1.250	0.0037	0.37
	0.35	1.297	0.0058	0.58
	0.40	1.344	0.0089	0.89
	0.45	1.389	0.013	1.3
	0.50	1.436	0.020	2.0
	0.55	1.484	0.030	3.0
	0.60	1.536	0.045	4.5
	0.65	1.591	0.069	6.9
	0.70	1.652	0.11	11
	0.75	1.723	0.18	18
	0.80	1.807	0.32	32
	0.85	1.916	0.64	64
	0.90	2.070	1.6	160
	0.95	2.347	7.2	720
	1.00	3.1	197	19700

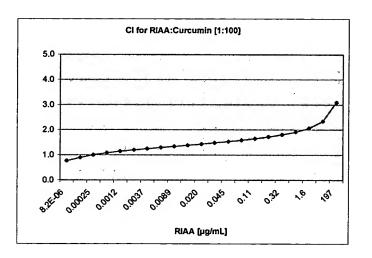


Figure 6H

Inventor: Babish et al. Filing Date: Herewith Attorney Client-Matter No.: 68911-074

Tel: 858-535-9001

RI/	AA:Caff	eine [100:1]		
			RIAA	Caffeine
_	Fa	CI	(µg/mL)	[µg/mL]
	0.02	483000	0.010	0.000
	0.05	23100	0.039	0.000
	0.10	2104	0.11	0.0011
	0.15	477	0.21	0.0021
	0.20	156	0.34	0.0034
	0.25	62	0.51	0.0051
	0.30	28	0.72	0.0072
	0.35	13	0.98	0.010
	0.40	6.715	1.3	0.013
	0.45	3.481	1.8	0.018 .
	0.50	1.829	2.3	0.023
	0.55	0.961	3.1	0.031
-	0.60	0.498	4.1	0.041
1	0.65	0.251	5.5	0.055
-	0.70	0.121	7.5	0.075
-	0.75	0.054	· '11	0.11
	0.80	0.021	16	0.16
	0.85	0.007	26 .	. 0.26
	0.90	0.002	. 49	0.49
	0.95	0.000	138	1.4

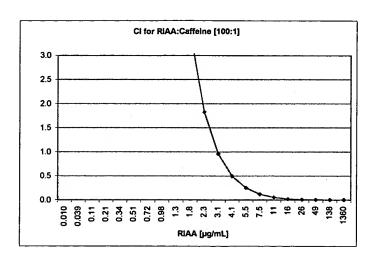
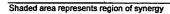


Figure 7A

RIAA:Caffei	ne [10:1]		
		RIAA	Caffeine
Fa	CI	(µg/mL)	[µg/mL]
0.02	25	0.0000054	0.000000
0.05	14	0.000023	0.000002
0.10	8.673	0.0005	0.000045
0.15	6.514	0.0029	0.00029
0.20	5.252	0.011	0.0011
0.25	4.396	0.036	0.0036
0.30	3.764	0.097	0.010
0.35	3.270	0.24	0.024
0.40	2.866	0.56	0.056
0.45	2.527	1.3	0.13
0.50	2.233	2.8	0.28
0.55	1.974	6.3	0.63
0.60	1.742	14.0	1.4
0.65	1.529	33.0	3.3
0.70	1.330	82.0	8.2
0.75	1.142	222	22
0.80	0.961	697	70
0.85	0.781	2787	279
0.90	0.596	17533 ***	1753
0.95	0.393	341940	34194
± 1.00	- 0.195	242070000	



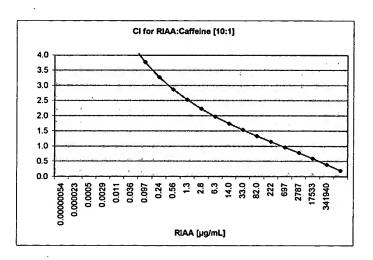


Figure 7B

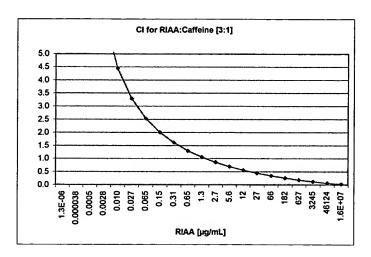
Inventor: Babish et al. Filing Date: Herewith

Attorney Client-Matter No.: 68911-074

Tel: 858-535-9001

RIAA:Caffeine [3:1]

		RIAA	Caffeine
Fa	CI	[µg/mL]	[µg/mL]
0.02	60	0.0000013	0.000000
0.05	22.000	0.000038	0.000010
0.10	10.324	0.0005	0.000
0.15	6.380	0.0028	0.001
0.20	4.442	0.010	0.002
0.25	3.296	0.027	0.007
0.30	2.540	0.065	0.016
0.35	2.006	0.15	0.037
0.40	1.609	0.31	0.078
0.45	1.303	0.65	0.16
0.50	1.060	1.3	0.33
0.55	0.863	2.7	0.67
0.60	0.700	5.6	1.4
0.65	0.584	12	3.0
0.70	0.448	27	8.8
0.75	0.348	66	17
0.80	0.262	182	48
0.85	0.187	627	157
0.90	0.121	3245	811
0.95	0.064	46124	11531
* 1.00	0.023	16236000	



Shaded area represents region of synergy

Figure 7C

RIAA:Caffeine [3:2]

			RIAA	Caffeine	
Fa		CI	[µg/mL]	[µg/mL]	
0.02 538000		0.012	0.005		
	0.05 21100		0.036	0.014	
	0.10	1640	0.088	0.034	
	0.15	337	0.15	0.059	
	0.20	103	0.22	0.089	
	0.25	39	0.31	0.124	
	0.30	16	0.42	0.167	
	0.35	7.534	0.55	0.218	
	0.40 3.645		0.70	0.281	
	0.45	1.818	0.89	0.357	
_	0.50	0.921	1.1 🦠 🦞	0.452	
	0.55	* * 0.467.	1.4 * 4	0.572	
k	0.60	0.234	1.8	0.728	
	0.65	0.114	2.3	0.920	
•	0.70	0,053	3.1 ** **	1.240	
	0.75	* 30.0230	s 4.1 m 8	¥1.640	
	0.80	0.009	5.8	2.304	
	0.85	0.0030	8.7	3.472	
**	0.90	0.0010	15	6,000	
	0.95	0.000062	· 36 · »	14.400	
	1.00	, 0.00000058	251	100,400	

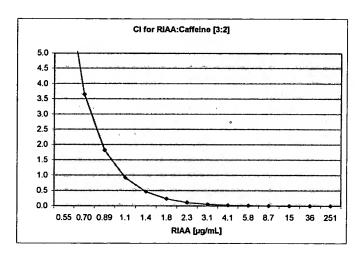


Figure 7D

Inventor: Babish et al. Filing Date: Herewith Attorney Client-Matter No.: 68911-074

Tel: 858-535-9001

AA:Caffeir	ne [1:1]		
		RIAA	Caffeine
Fa	CI	(µg/mL)	[µg/mL]
0.02	0.176	0.0000000038	0.00000
0.05	0.209	0.00000035	0.00000
0.10	0.241	0.000013	0.0000
0.15	0.263	0.00011	0.00011
0.20	0.281	0.00060	0.00060
0.25	0.298	0.0024	0.0024
0.30	0.313	0.0079	0.0079
0.35	0.328	0.024	0.024
0.40	0.343	0.065	0.065
0.45	0.359	0.17	0.17
0.50	0.376	0.45	0.45
0.55	0.394	1.2	1.2
0.60	0.415	3.2	3.2
0.65	0.438	8.7	8.7
0.70	0.467	26	26
0.75	0.504	86	86
0.80	0.554	341	341
0.05	0.000	4000	4000

1805

16460

584650

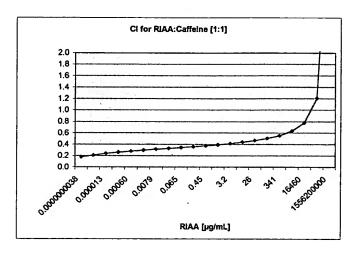
1556200000

1805

16460

584650

1556200000



1.206 5.041 Shaded area represents region of synergy

0.632

0.779

0.85

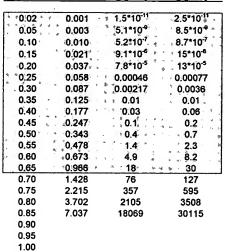
0,90

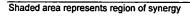
0.95

1.00

Figure 7E

		RIAA	Caffeine
Fa	CI	[µg/mL]	[µg/mL]
* *0:02 * *	0.001	* 1.5*10 ⁻¹¹	2.5*10**
0.05	0.003	* [5,1*10*	8.5*10* *
0.10	0.010	5.2*10*7.	8.7*10 ⁻⁷
0.15	0.021	9.1*10-6	15*10 ⁻⁶
∘0.20	0.037	7.8*10.5	. 13*10 ⁻⁵
* *0 25	0.058	0.00046	0.00077





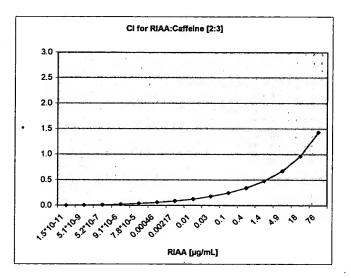
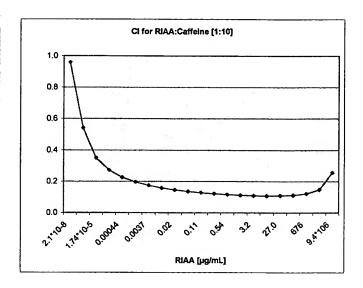


Figure 7F

Inventor: Babish et al. Filing Date: Herewith Attorney Client-Matter No.: 68911-074 Tel: 858-535-9001

RIAA:Caffeine [1:10]

NIAM. Call	::::e [1. 10]		
		RIAA	Caffeine
Fa	CI	(µg/mL)	[µg/mL]
0.02	0.958	2.1°10 ⁻⁸	2.1*10-7
0.05	0.542	8.9*10 ⁻⁷	8.9*10 ⁻⁶
0,10	0.351	1.74*10 ⁻⁵	1.74*10-4
0.15	0.272	0.00011	0.0011
0.20	0.227	0.00044	0.0044
0.25	0.197	0.0014	0.014
0.30	0.175	0.0037	0.037
0.35	0.159	0.01	0.09
0.40	0.147	0.02	0.2
0.45	0.137	0.05	0.5
0.50	0.128	0.11	1.1
0.55	0.122	. 0.24	2.4
0.60	0.117	0.54	5.4
0.65	0.113	1.3	13
0.70	0.110	3.2	32
0.75	0.109	8.6	-86
0.80	0.110	27.0	270
. 0.85	0.113	107	1070
0.90	0.122	676	6760
0.95	0.148	13202	132020.000
1.00	0.258	9.4*10	9.4*107



Shaded area represents region of synergy

Figure 7G

RL	٩А	:Ca	ffei	ine	[1	:1	00]	

		RIAA	Caffeine
Fa	CI	[µg/mL]	[µg/mL]
0.02	0.003	5.7*10-11	· · 5.7*10 ⁻⁹
0.05	0.005	6.7*10 ⁻⁹	6.7*10 ⁻⁷
0.10	0.008	2.9*10-7	2.9*10 ⁻⁵
0.15	0.013	2.9*10 ⁻⁶	2.9*10-4
0.20	0.017	1:7*10-5	1.7*10-3
0.25	0,023	7.1*10-5	7.1*10-3
0.30	0.031	0.00025	0.025
0.35	0.040	0.0008	0.08
0.40	0.051	0.0023	0.23
0.45	0.066	0.0065	0.65
0.50	0.085	0.018	1.8
0.55	0.110	0.049	4.9:
0.60	0.143	0.14	13.7
0.65	0.190	0.40	40.1
0.70	0.259	1.3	126
0.75	0.365	4.5	446
0.80	0.543	. 19	1900
0.85	0.882	109	10900
0.90	1.693	1116	111600
0.95		47705	4770500
1.00			

Figure 7H